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(54) Title: PHARMACEUTICAL PREPARATION FOR INHALATION OF AN OPIOID

(57) **Abstract**

The present invention relates to the inhalation of opioids, such as morphine, administered as a dry powder. Opioids administered as dry powder for inhalation are intended for local treatment in the respiratory tract, or for systemic treatment following absorption in the lungs and airways. Indications for opioids dry powder per inhalation include the treatment of dyspnoea and pain. Opioids as dry powder for inhalation may be administered with the use of an inhaler, which can be described as a multi–dose reservoir system such as the Cyclovent™, or a premetered single–dose system such as the Cyclohaler™, or a premetered disposable system as the Disphaler™.

Pharmaceutical preparation for inhalation of an opioid.

The present invention relates to the inhalation of opioids, such as morphine, administered as a dry powder.

The pharmacologic properties of opioids include effects on the central nervous system and the bowel and include analgesia, drowsiness, changes in mood, respiratory depression, reduced gastrointestinal mobility, nausea, vomiting, and miosis.

BACKGROUND OF THE INVENTION

Opioids are mainly used for the relief of moderate to severe pain. In addition, reports have been published on the use of opioids in the treatment of dyspnoea and neurally mediated mucus secretion.

In the treatment of pain as well as dyspnoea, opioids are administered parentally and orally. Inhalation of nebulized opioids solutions has been reported to be effective with lower doses and less side effects, as compared to the parental and oral route of administration. As nebulizers are widely used in clinical practice, morphine is frequently administered by the nebulized route. Reference is in this respect made to Farncombe M. Chater S and Gillin A, "The use of nebulized opioids for breathlessness: a chart review," Palliative Medicine 1994: 8; 306-312, and to Farncombe M and Chater S, "Clinical application of nebulized opioids for treatment of dyspnoea in patients with malignant disease," Support Care Cancer 1994: 2; 184-187.

The use of solutions for inhalation administered by a nebulizer has several drawbacks, such as escape of vapour through the mask during expiration and trapping of the nebulizer solution in the nebulizer. Also to inhale by means of a nebulizer takes some time, which can be aggravating for terminally ill patients.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a

convenient and reliable method of administering opioids. More specifically, the administration is by inhalation.

The invention therefore relates to a pharmaceutical preparation for inhalation consisting of micronized particles of an opioid having a fine particle fraction of at least 10%.

For administration by inhalation, the compositions according to the invention are conveniently delivered by conventional means, e.g. in the form of a single-dose premetered system such as the Cyclohaler™ using cartridges, or a premetered disposable inhaler such as the Disphaler™, or in the form of a multidose reservoir system such as the Cyclovent™.

Examples of the pharmacologically active substances as described in general as opioids are morphine, hydromorphone, oxymorphone and codeine. Morphine is the preferred substance. The substances can be used in the form of their salts, sich as alkali metal or amine salts or as acid addition salts; or as esters such as lower alkyl esters, or as solvates (hydrates), to optimise the activity, efficacy and/or stability of the substance. Morphine sulphate and morphine hydrochloride are the preferred salts to be used according to the invention.

In order to optimize or to control the properties of the inhalation powders it is sometimes useful to add excipients, which are pharmaceutically suitable and physiologically harmless. Examples of such excipients include monosaccharides (such as glucose and arabinose); disaccharides (such as lactose, saccharose and maltose); polysaccharides (such as dextrans); polyalcohols (such as sorbitol, mannitol and xylitol); salts (such as sodium chloride and calcium carbonate) or mixtures of these excipients with one another. Lactose is the preferred excipient.

EXPERIMENTAL PART

For dry powder inhalation systems the patient inspiratory effort through the device is the main force delivering and aerosolizing the formulation. Upon

inspiration the agglomerates or aggregates, which are formed during processing, should break apart and present the drug as more or less discrete particles for inhalation into the lung.

In order to document the dispersion characteristics, as a function of the inhaled air flow rate, *in vitro* performance test with the use of a impinger are performed. The basic mechanism in this experiment is impaction and the apparatus consists of several stages. The stages represent parts of the respiratory tract. In this manner the powder aerosol is characterized, in the sense of particle size distribution, on the basis of the aerodynamic behaviour of particles. The respirable fraction of a powder is defined as the mass of the particles with a diameter less than 6,8 μm. This respirable fraction is reflected in the determination of the fine particle dose (in mg) or the fine particle fraction (% relative to the delivered dose, defined as the sum of all stages of a impinger and the throat).

The above characterization of a preparation meets the standards of the "Inhalanda" Monograph of the European Pharmacopeia, as published in Pharmeuropa 1996, p. 245-258.

EXAMPLES

Preparation of the mixtures

Morphine sulphate BP was micronized using an air jet mill (LS 100, GfM) at a pressure of 4 bar and a feed rate of 5 g/min. The particle size distribution was determined using a laser diffraction particle sizer (Malvern Mastersizer X). A mixture with lactose monohydrate was obtained by using a high-shear mixer (Robot Coupe R2) during 5 minutes. The ratio of morphine sulphate:lactose in the obtained mixture was 1:17. This mixture was used to fill the cartridges for the Cyclohaler (Example 1), to fill the Cyclovent (Example 3) and to fill the Disphaler (Example 5). All dosages weighted 25 mg. In addition pure micronized morphine sulphate was used to fill the cartridges for the Cyclohaler (Example 2), to fill the Cyclovent (Example 4) and to fill the Disphaler (Example 6). These dosages weighted 10 mg.

Characterization of the aerosol formulations

For determination of the fine particle fraction all inhalation means were characterized by using a multi-stage liquid impactor (Copley, UK) made from glass and metal having four impaction stages and a filter (PA/PH/Exp. 12/T (96) 11 ANP). The nominal cut-off diameter of the stages is 13 μm, 6.8 μm, 3.1 μm and 1.7 μm at the operating air flow rate of 60 ± 5 litres per minute. A total volume of 4 litres of air was applied. In the tests with the Cyclohaler, 10 doses were sampled. However, in the tests with the Disphaler and Cyclovent 5 doses were sampled. All stages including the filter, the throat were analyzed on morphine sulphate by using a high performance liquid chromatography (HPLC) method. The HPLC method was performed by using a Symmetry C18 250 x 4.6 mm ID column (Waters, Milford, Massachusettes, USA), a mobile phase of acetonitrile:water (50:50) with 0.1 M sodium lauryl sulphate and 0.04 M potassium hydrogen phosphate dissolved in water, and a UV detector set at 287 nm. All samples were dissolved in acetonitrile:water (50:50). All calculations were related to morphine as a free base.

EXAMPLE 1

Cyclohaler	
	mg morphine
throat	0,12
stage 1 (< 13 μm)	0,30
stage 2 (< 6,8 μm)	0,10
stage 3 (< 3,1 μm)	0,24
stage 4 (< 1,7 μm)	0,16
filter	0,04
fine particle dose: 0,44 mg morphine	
fine particle fraction: 46 % (= respirable fraction; < 6,8 μm)	

EXAMPLE 2

Cyclohaler	
	mg morphine
throat	0,70
stage 1	1,40
stage 2	0,67
stage 3	1,31
stage 4	0,73
filter	0,29
fine particle dose: 2,33 mg morphine	
fine particle fraction: 46 %	

EXAMPLE 3

Cyclovent	
	mg morphine
throat	0,20
stage 1	0,26
stage 2	0,10
stage 3	0,23
stage 4	0,17
filter	0,06
fine particle dose: 0,46 mg morphine	
fine particle fraction: 45 %	

EXAMPLE 4

Cyclovent	
	mg morphine
throat	0,55
stage 1	0,40
stage 2	0,20
stage 3	0,49
stage 4	0,59
filter	0,50
fine particle dose: 1,58 mg morphine	
fine particle fraction: 58 %	

EXAMPLE 5

Disphaler	
	mg morphine
throat	0,23
stage 1	0,39
stage 2	0,08
stage 3	0,20
stage 4	0,12
filter	0,04
fine particle dose: 0,36 mg morphine	
fine particle fraction: 34 %	

EXAMPLE 6

Disphaler	
	mg morphine
throat	1,72
stage 1	3,99
stage 2	0,38
stage 3	0,43
stage 4	0,17
filter	0,11
fine particle dose: 0,71 mg morphine	
fine particle fraction: 10 %	

The formulation administered by the described means and according to the present invention shows good dispersion characteristics, as reflected by adequate fine particle doses. This indicates that various parts of the respiratory tract can be reached. Thus diseases and illnesses in these parts of the respiratory tract can be treated adequately. Furthermore, patients with poor lung function are able to inhale the formulations according to the invention and administered by the described modes.

C L A I M S

1. A pharmaceutical dry-powder composition suitable for inhalation consisting of micronized particles of an opioid having a fine particle fraction of at least 10%.

2. A pharmaceutical dry-powder composition according to claim 1, wherein said opioid is selected from the group consisting of morphine, hydromorphone, oxymorphone and codeine.

3. A pharmaceutical dry-powder composition according to claim 1 or 2, wherein said opioid is in the form of a salt, an ester or a solvate.

4. A pharmaceutical dry-powder composition according to claim 3, wherein said salt is an alkali metal salt, amine salt or an acid addition salt, said ester is a lower alkyl ester, and said solvate is a hydrate.

5. A pharmaceutical dry-powder composition according to any of the claims 1 to 4 and a pharmaceutically acceptable carrier.

6. A pharmaceutical dry-powder composition according to claim 5, wherein said carrier is selected from the group consisting of mono-, di- and polysaccharides; polyalcohols; salts and mixtures thereof, preferably lactose.

7. Use of an opioid having a fine particle fraction of at least 10% for the preparation of an inhalation medicament for the treatment of dyspnoea and pain.

INTERNATIONAL SEARCH REPORT

	International Application No PCT/NL 98/00713

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K31/485 A61K9/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 35562 A (WATTS PETER JAMES ;DANBIOSYST UK (GB); ILLUM LISBETH (GB)) 2 October 1997 (1997-10-02) examples 5,9 claims 8,10,18 ---	1-7
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X	WO 97 17948 A (EURO CELTIQUE SA ;ALFONSO MARK (US); GOLDENHEIM PAUL (US); SACKLER) 22 May 1997 (1997-05-22) page 7, line 30 - page 9, line 3 --- -/--	1-7

[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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INTERNATIONAL SEARCH REPORT

Ir. ıtional Application No
PCT/NL 98/00713

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

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